

Support Care Cancer (2011) 19 (Suppl 1):S49–S55
DOI 10.1007/s00520-010-1036-1

SPECIAL ORIGINAL ARTICLE

Antiemetic research: future directions

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Received: 21 October 2010 / Accepted: 22 October 2010 / Published online: 10 November 2010
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Abstract

Purpose and methods As a part of reviewing the Multinational Association of Supportive Care in Cancer (MASCC) antiemetic guidelines in Perugia in 2009, an expert group identified directions for future antiemetic research.

Results and conclusions In future trials, the prediction of nausea and vomiting may combine algorithms based on observed prognostic factors relating to the patient and the

anticancer therapy, the identification of the genes that code for receptors, and pharmacogenetic studies of the metabolism of drugs. Design issues for future trials include standardising the emetic stimulus across studies and finding the minimum tolerated effective dose and schedule of an antiemetic. Also control of delayed emesis is not independent of the control of acute emesis. The full range of side effects and the impact on global quality of life scores should be part of the routine assessment of an antiemetic. With current high rates of control of acute vomiting, future trials will need to consider new primary endpoints such as nausea, a complex symptom, where improvement is needed. Economic endpoints should be incorporated to ascertain the cost benefit of antiemetic prophylaxis, taking into account the impact of nausea on work capacity. New antiemetic drugs may be targeted at different receptors, such as opioid, cannabinoid and peptide YY receptors. New research is needed into determining the extent of corticosteroid use. The emetic potential of a range of newer cytotoxics particularly when used in combinations and different scheduling, such as prolonged oral dosing of cytotoxics and use of targeted therapies, are all areas in need of research. More antiemetic studies are needed in niche areas such as in patients receiving high dose chemotherapy, radiation therapy or combined modality therapy. Further evidence of the efficacy of newer antiemetic agents is required in children.

Keywords Antiemetics · Future research · Methodology · Chemotherapy · Nausea · Vomiting

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Introduction

In 2009, a meeting was held in Perugia in Italy to revise the MASCC antiemetic guidelines. Experts review the litera-

ture and produce guidelines according to the available evidence or by consensus if the evidence is poor. One committee is charged with identifying areas where future research would be most fruitful.

Although the control of both acute and delayed vomiting after anti-cancer chemotherapy is satisfactory in the majority of patients due to the combination of a 5-hydroxytryptamine 3 receptor (5-HT₃) antagonist, dexamethasone and a neurokinin 1 receptor (NK₁) antagonist, there are still specific areas requiring further research. With gene arrays and pharmacogenomics, we should have an opportunity to create better algorithms for predicting emesis. Nausea, a term which covers subjective feelings, is not controlled as well as vomiting. Data on emesis risk and the need for antiemetic prophylaxis have not been well researched with new drugs, targeted therapies and prolonged oral therapy. New receptors are targets for new antiemetic drugs and functional imaging will refine dosing strategies. We need to improve our creation and dissemination of guidelines.

Prognostic factors

Factors predicting who would vomit after chemotherapy have been identified over decades of antiemetic studies. The emetic potential of the drugs in the chemotherapy regimen, which in turn depends on their doses and schedules resulted in them being classified into groups of those with minimal, low, moderate or high risk of causing emesis if left untreated [18]. The emetic potential of combinations of drugs were more problematic to classify, due to the limited data available. For example, the combination of an anthracycline and cyclophosphamide, both of which have moderate emetic potential, results in a regimen of high emetic potential. Furthermore, the emetic risk classification does not include nausea.

There were also patient characteristics which were associated with a propensity to experience emesis post chemotherapy. There was more difficulty controlling post-chemotherapy emesis in females, younger patients did not respond as well to antiemetics, and a history of prior alcohol intake of greater than 100 g/day was associated with less emesis following cisplatin chemotherapy [10, 38, 42, 43]. The reason for these observations could still be a useful area for further research. It is noteworthy, that addition of the NK₁ receptor antagonist, aprepitant, to a combination of ondansetron and dexamethasone, seemed to negate the adverse prognostic effect of female gender on the prevention of chemotherapy-induced vomiting. With addition of aprepitant 66% of women and 69% of men were protected from emesis and did not need rescue medication after cisplatin-based chemotherapy, whereas only 41% of women as compared to 53% of men were protected without aprepitant [17]. The physiological or pharmacological

mechanisms of such gender differences, for example the influence of hormonal status, would be worth exploration.

Other factors being explored, are the susceptibility to motion sickness or the setting of the chemotherapy [32]. Furthermore, low emotional or role functioning, past history of morning sickness, anxiety, expectations for developing nausea/vomiting during chemotherapy or vestibular dysfunction have also been identified as key risk factors [31, 37, 50]. Further psychosocial factors need to be explored, as does the issue of whether the expectation of nausea and vomiting is correlated with its occurrence [19, 35].

Although clinical decision-making may be aided by creating an algorithm based on these prognostic factors for emesis, new genetic factors being investigated may make the prediction of emesis and selection of antiemetics and their doses more accurate. The emergence of gene array technology identifying the genes coding for the 5-HT₃ and NK₁ receptors may allow clinical correlations and more rational selection of antiemetic regimens for patients. For example, patients with genetic variations in the 5-HT_{3B} receptor gene might respond differently to antiemetic treatment with the 5HT₃ receptor antagonists [46].

Pharmacogenetic studies investigating functional genetic polymorphisms involving serotonergic, dopaminergic and neurokinin systems may allow more rational drug and dose selection for individual patients. For example, the efficacy of antiemetic treatment with some 5HT₃ receptor antagonists (e.g. tropisetron) depends on cytochrome P-450 2D6 (CYP2D6) genotype, and rapid and ultrarapid metabolisers could be undertreated [23]. Ultrarapid metabolisers could, however, benefit from treatment with a 5-HT₃ antagonist not dependent of the CYP2D6 enzymes (e.g. granisetron).

Design issues in clinical trials

The randomised controlled double blind parallel design has been the gold standard for antiemetic studies, and will continue to be so, but there are issues to be resolved in the design of future trials. For example, the studies will have to be controlled for the new prognostic factors suggested above.

Another issue is standardising the emetic stimulus across studies. Cisplatin at greater than 50 mg/m² has been the standard upon which regimens of high emetic potential have been based, but there has been confusion about the combination of an anthracycline and cyclophosphamide, two drugs of moderate emetic potential, which in combination become a regimen of high emetic potential.

When studying delayed emesis the response rate to an antiemetic may be influenced by the control of the acute phase of emesis. In the pivotal studies of aprepitant as part of a triple antiemetic regimen with a 5HT₃ receptor

antagonist and dexamethasone, the NK₁ receptor antagonist was always used in the acute phase and then continued to cover the delayed phase. Palonosetron with its longer duration of action also was commenced in the acute phase. The response in the acute phase does influence the control of delayed emesis [2].

Side effects that are particularly due to a new antiemetic can be difficult to ascertain when antiemetics are given in combinations and the side effects of the cytotoxic therapy are also present. It is important to broadly record side effects so that unexpected effects are not missed. It is only in recent trials, for example, that a link between the use of aprepitant and increases in neutropenia and febrile neutropenia have been reported although this has not been confirmed in other studies [13]. The measurement of quality of life gives an overall assessment of the impact on the antiemetic on the wellbeing of the patient. This is particularly important not only because it serves to balance the efficacy and toxicity of the antiemetic but also because emesis impacts on other aspects of quality of life such as fatigue, appetite and sleep disturbance [26].

With response rates in acute vomiting approaching 90% in chemotherapy-naïve patients with triple antiemetic prophylaxis, it will be increasingly difficult to demonstrate a clinically meaningful benefit for a new agent looking at the first course of chemotherapy only. Therefore it can be useful to monitor the entire course of chemotherapy (4–6 cycles), when a new drug is investigated. The cut off for clinically meaningful improvement in patient reported outcomes has been suggested as 10%, with the lowest estimate being 7% [7, 36]. Different endpoints in future studies are desirable. The most obvious of these is nausea which is not as well controlled as vomiting [30]. Nausea is an entity which encompasses different subjective and objective experiences and needs to be better defined in order to address it properly in future studies [40].

In time it may be possible to incorporate functional endpoints such as the effective blockade of receptors as demonstrated by PET scan which may allow early prediction of efficacy, as discussed below.

Economic endpoints should be part of randomised trials of new antiemetics and combinations. These are best measured prospectively and design issues discussed with health economists. It is important to ascertain the minimal effective dosing and scheduling of antiemetics [5, 25, 52]. This not only improves the therapeutic index but the cost efficacy ratio.

Other design issues include the measurement of efficacy over multiple cycles to see if there is any change in efficacy of the antiemetic regimen over time. The methodological challenges of evaluating antiemetic therapy over multiple cycles are well documented [14]. These studies are best done in patients with tumour types which will minimise the

dropout rate. Patients dropping out can change the balance of prognostic factors over time. Also, statistical techniques need to account for the antiemetic efficacy in a particular cycle being influenced by the response in the previous cycle [42]. There is also a need to specifically explore regimens which will rescue that small percentage of patients who do not respond to the established antiemetics. Such patients can be pre-randomised to a particular rescue regimen if required or entered onto a study if they fail to respond to an antiemetic regimen given as prophylaxis prior to the first cycle of therapy.

Usage of corticosteroids

Corticosteroids such as dexamethasone are mentioned in guidelines as prophylaxis against chemotherapy of low emetic potential when administered as monotherapy, and are used to prevent vomiting and nausea in either chemotherapy of moderate or high emetic potential due to their synergistic efficacy in combination with other antiemetics. In guidelines, the scheduling and dosing of corticosteroids is tailored by taking into account the therapeutic setting and not the patient's characteristics, which are of importance. However, the clinician must consider that their administration may be associated with a range of side-effects, which may increase when administered as part of multiple-day antiemetic regimens [48]. A recent survey investigating moderate to severe side-effects associated with dexamethasone administered for prophylaxis against delayed CINV after MEC included insomnia (45%), gastrointestinal symptoms (27%), agitation (25%), increased appetite (18%), weight gain (17%), skin rash (15%) and depression (7%) [48]. For these reasons, there is a particular interest in reducing their administration in certain clinical situations and/or in certain subsets of patients. Thus recently one double-blind study and one open-label study in patients receiving palonosetron plus dexamethasone on day 1 randomly assigned to receive either placebo or dexamethasone on days 2 and 3 have shown that there is an opportunity to reduce the total corticosteroid dose with no loss of efficacy in delayed MEC, although some patients experience an increase of nausea on some periods of observation [1, 6].

It should be noted that present guidelines, based on the fact that steroids were not used on days 2 and 3 of aprepitant containing antiemetic regimes when patients received AC like chemotherapy do not advocate the use of steroids for prevention of delayed nausea, while the studies showed that up to 50% of the patients suffered from nausea. This paradox will need further study in the setting of single day antiemetic regimens, which are highly effective in emesis control, but also seem to lose on control of nausea over several days [16].

New antiemetics

There are some drugs such as olanzapine which act on multiple receptors and are only just being investigated for post-chemotherapy emesis. Olanzapine is a thienobenzodiazepine which acts on multiple receptors including dopamine, serotonin, adrenergic, muscarinic and histamine receptors and has shown antiemetic activity in small studies with serotonin antagonists and steroids in both acute, and delayed emesis [33, 44].

The advent of the NK₁ receptor antagonists demonstrated the utility of functional imaging of NK₁ receptors by PET scan [15]. Techniques are evolving which can not only visualise where the receptors are, but quantitate them, and this will enable non-invasive methods of studying the binding of NK₁ receptor antagonists [34]. Such functional imaging can be used in developing new agents such as NK₁ receptor antagonists which bind with higher affinity and will have a longer duration of action [21]. PET scans with appropriate labelled markers can be used to investigate different neurotransmitters and address issues like the optimal duration of receptor occupancy for antiemetic efficacy or the relative importance in acute or delayed emesis of central as compared to peripheral receptors.

There are still many possibilities for new anti-emetic agents to be developed as new receptor families are further investigated. The mu opioid receptors, for example, may mediate an antiemetic response in humans [41]. The cannabinoid CB1-receptor agonists possess broad-spectrum antiemetic activity in animal models in both chemotherapy and radiation therapy induced emesis [8, 47]. The synthetic cannabinoids nabilone and levonantradol have proven antiemetic activity in humans but side effects limit their usefulness [45, 49]. Studies of peptide YY and its analogues and its binding sites may result in a new class of antiemetic strategies [24].

New research

Nausea

We have suggested nausea as one of the primary endpoints for future studies because it has a much higher impact on daily living than vomiting and because it will be possible to more easily measure improvements but is not well controlled by present antiemetic regimens. Nausea is often present without the presence of vomiting, and hence these two symptoms are related but distinct phenomena. However, the subjective side effect of nausea in its own right needs further study. As a side effect it has the three components of severity, duration and frequency, which should be reported. However nausea is a subjective sensation which can only be reported by the patients who have been found to be reporting a

complex array of symptoms ranging from anorexia to indigestion with nausea perhaps being only part of a symptom cluster [30]. More qualitative research is required to define the range of symptoms that patients report as nausea, so that a range of treatments in addition to antiemetics can be employed if necessary. A recent study in rats found that hypothalamic ghrelin decreased markedly 24–48 h after cisplatin and that intracerebroventricular injection of ghrelin was able to reverse the cisplatin-induced decrease in food intake. Furthermore the decrease in ghrelin secretion seemed to be caused by stimulation of 5-HT₂ receptors, because a 5-HT₂ receptor antagonist was able to enhance ghrelin secretion and to suppress cisplatin-induced anorexia [51]. Nausea may have different targets that may require the identification of new and unique receptor pathways. This may provide insights into other symptoms such as anorexia which may cluster with it.

Time course and severity of emesis, secondary antiemetic and new drug delivery systems

It should be routine in the development of new anticancer agents that the intensity and duration of emesis is determined to optimise the use of prophylactic antiemetics. More recent drugs in common usage such as oxaliplatin and pemetrexed require better characterisation of their emetic potential in combination therapies, as indeed other commonly used combination chemotherapy agents. Hence there is a need for more observational prospective data characterising the course of nausea/vomiting over several cycles to obtain more information on the emetic potential of combination drugs, which will help in an improved classification of the emetic potential of these drugs. This is also true for low and minimally emetic chemotherapy, where the data available is insufficient to guide practice and a particular focus should be directed to antiemetic control in patients receiving such chemotherapy; the assessment of the effectiveness of some 'secondary' antiemetics in this lower emetic risk group may be appropriate. Furthermore, the role of 'secondary' antiemetics (i.e. benzodiazepines, anticholinergics etc.) in combination with 'standard' antiemetics or as rescue medications is not well established, although they are used very frequently in everyday practice, and this may be another area of research focus in the future. An improved generation of such secondary antiemetics may also be a future research endeavour. Cytotoxic drugs delivered by prolonged oral administration such as capecitabine or temozolomide have not had the time course of their associated emesis well documented, and no evidence based recommendations for prophylactic antiemetics can be recommended. A similar situation exists for targeted therapies such as imatinib, which are also administered by prolonged oral dosing. Recording the emesis will require

modification of the patient diary tools which were initially designed for intermittent dosing. Assessment of nausea/vomiting should be improved in future studies, and the use of well validated and sensitive multidimensional tools should be carefully considered. Use of the same tool across studies will facilitate in the future the possibility of comparisons. MASCC has developed and validated such a tool [27] and a comprehensive review of the quality and psychometric properties of all tools available to date to measure nausea/vomiting is available [4].

While the intravenous and oral administration of antiemetics is well established, other delivery systems, such as the granisetron transdermal patches [3] which are available in some countries such as the USA and Australia, may offer more patient choice, can be convenient, reduce pill counts and be particularly useful where compliance to medication is low, where there are swallowing difficulties or where oral absorption may be compromised. Such delivery systems need further research.

Niche groups

There are specific treatment groups where evidence is still required about the optimal antiemetic therapy. Patients receiving high dose chemotherapy prior to haemopoietic rescue or multiple day chemotherapy of high emetic potential require better control of emesis. Children's responses to antiemetic combinations should not just be extrapolated from adult studies, because they have a different propensity to vomit, are receiving different regimens, and may respond differently to various classes of antiemetics. The elderly people with cancer should be a special focus of future antiemetic research, considering their comorbidities, polypharmacy, self care abilities, costs, decreased renal and hepatic function affecting drug metabolism and excretion [20]. Finally there is a great need for further research into the emesis associated with patients receiving radiation therapy with multiple doses and multiple fields, with and without concomitant chemotherapy.

Non-pharmacological adjuvant interventions

While the views of clinicians on the use of non-pharmacological approaches to the management of nausea/vomiting may be mixed, such use as adjuvants to antiemetics may lead to an improved control of symptoms. There is strong evidence that electroacupuncture can significantly improve chemotherapy related nausea/vomiting [12] and that use of acupressure wristbands can have a protective effect in chemotherapy-induced [12, 28] and radiotherapy-induced nausea/vomiting [39], although the acupressure results are mixed and their role as single antiemetic interventions in

low/minimally emetogenic chemotherapy is unclear. Other potential useful non-pharmacological interventions include hypnosis, dietary management or distraction (particularly in children) that have shown promise, but more concrete evidence from randomised trials is necessary. Cognitive behavioural interventions are appropriate for the management of anticipatory nausea/vomiting, and indeed recommended by MASCC guidelines, although studies in other areas of antiemetic control are almost nonexistent and our understanding of the effects of such treatments needs improvement.

Guidelines

Studies in new methodologies for guidelines including literature searching, consulting, disseminating and updating are needed. Antiemetic guidelines are published by several groups including MASCC, ASCO and NCCN [22]. The differences in the guidelines often relate to when they are updated and therefore encompass the latest literature. There is very little evidence that has been collected on the efficacy of the dissemination of antiemetic guidelines or their uptake, and their subsequent impact on clinical practice although a prospective study has provided some initial evidence that patients receiving antiemetics based on such guidelines had an improved control of nausea/vomiting compared to those who did not receive guideline-consistent antiemetics, and also there was significant cost savings in the guideline consistent group [29]. A few trials indicate that only around 50% of patients receive antiemetic prophylaxis as recommended by guidelines. Lack of implementation may be one of the greatest obstacles to effective prophylaxis of nausea and vomiting, because patients do better, when they are receiving guideline recommended antiemetic therapy [11]. More research, however, is required in this area.

MASCC has taken a multinational approach and has standing committees responsible for sections of the guidelines, which can be updated on the web-based version every 6 months, whilst a major revision occurs in an intensive review process every 4 years.

A fruitful research area which is being explored by Cancer Council Australia for guidelines in general, is the use of a Wiki platform. This would allow for wide consultation and dissemination, and guidelines could be updated as new evidence becomes available. It is possible to search the literature electronically for antiemetic trials which could be fed as text into the wiki as they are published for an expert panel's comments and decision about whether the new evidence warrants a change in the guidelines. Research will be required to see if this is a cost effective method for keeping guidelines constantly updated.

Conclusions

Despite the success of the two new classes of antiemetic drugs, the 5HT₃ receptor antagonists and the NK₁ receptor antagonists in preventing acute and delayed post chemotherapy vomiting there is still much to be achieved in the prediction and treatment of emesis. The understanding of the nature of nausea and more trials to discover how best to control it, are still required. All new drugs and targeted therapies should have their emetic potential defined and the control of emesis with high dose and prolonged oral scheduling requires new studies. More antiemetic trials are needed for radiation induced emesis and in the paediatric age group. Furthermore, combined chemoradiation has become standard therapy of many cancer diseases and randomised antiemetic trials are highly warranted in this setting. The potential of new antiemetics targeted at different receptors such as opioid or mu receptors may see emesis continue to be perceived as less of a problem for patients facing chemotherapy [9].

Conflict of Interest The authors of this paper are all members of Multinational Association of Supportive Care in Cancer (MASCC) but have no financial interest or conflict of interest with regards to the content of this manuscript.

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